APPENDIX II

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Review

Electrical Stimulation of Skin

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In the United States each year there are estimated to be 2.5 million burn wounds, 30 million lacerations, and 6 million abrasions that are serious enough to require treatment.[1] A few of these injuries have been treated with electrical stimulation, and it has shown some promise to accelerate the healing process and perhaps to reduce the incidence of infection. Experimental electrical stimulation has been evaluated for the treatment of burns,[2-4] decubitus ulcers,[5-9] indolent ulcers,[2,10] ischemic ulcers,[11] diabetic nonhealing lesions,[12,13] surgical wounds,[14] keloid scars,[15] edema,[16] tumors,[17,18] hemorrhage and clotting,[19] skin infections,[20] and nonspecific skin wounds.[2,10,21-24]

Background

Twenty years after the first clinical trial, electrical stimulation is still rarely used as a clinical treatment for skin wounds.[12] There are a variety of reasons for this. Not all of the experimental studies concluded that electrical stimulation was beneficial to skin healing. More importantly, the literature has been ambiguous about the parameters for treatment, and little has been done to resolve these ambiguities. There are many parameters available to characterize or control a study, and the published reports often do not sufficiently describe them. Because standard parameters have not been developed, it is difficult to compare studies from different laboratories. Most importantly, the parameters that define the dose have never been established. Consequently, it is virtually impossible to compare previous studies in a meaningful fashion to draw useful conclusions about their comparable efficacies.

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Prospectively and retrospectively, it is possible to resolve these sources of ambiguity. It is possible to assess the nature of electrical stimulation and arrive at a set of parameters that allow reproducibility. We suggest two standard electrical parameters to render these studies electrically reproducible and suitable for comparison: average spatial current density and equivalent duty cycle, which are described herein. These parameters define the electrical stimulation in terms of the dosage and the dose rate per unit area during treatment. Although this defines the electrical parameters, there are still many treatment variables that must also be reported, ie, length of treatment and depth of wound. This review attempts to standardize the electrical parameters to allow for reproducibility of the stimulation studies.

The most common reason for nonreproducibility is failure to report the electrode size. Reporting of current intensity alone is rather meaningless without the electrode size. The electrode area and current can be combined to yield the average spatial current density (referred to as the current density). Current density defines the amount of current per unit of area. If the current output is 10 amperes and the electrode is 10 cm^2, then the current density is equal to 1 ampere (A)/cm^2. This parameter can be used with great flexibility. A researcher can compare previous studies on terms of current density. Consequently, progress can be made toward arriving at optimal parameters. Knowledge of the optimal current density allows the clinician to set the current on the equipment according to electrode size. All the clinician needs to do is multiply the average spatial current density by the electrode area and set the equipment to the new current output. It has been reported that current density is the best indicator of the electrochemical effects of

stimulation; it especially affects bacterial growth,[25] skin irritation, and burns.[26]

A second source of difficulties arises with time-varying currents. These currents may be exponentially decaying, pulsatile, or sinusoidal. When such a current is delivered, there are several ways of reporting the parameters. Traditionally, pulsed current was reported in terms of pulse width, frequency, waveform, and either peak or average current delivered. These parameters may be condensed into the term, equivalent duty cycle. The equivalent duty cycle expresses the percent of time an equivalent current is being delivered during treatment at the maximum amplitude of the actual current. In other words, instead of reporting the frequency of pulses, the duration of pulses, and the current delivered by each pulse, it is easier to report the equivalent percent of time the current is being delivered at its peak.

TABLE 1. *Literature Review*

Reference	Model	Current Density (mA/cm²)	Polarity	Duty Cycle/ Waveform	Treatment (hours/ days)	Results/Measurement	Proposed Mechanism
Bolton[25] (1980)	Humans	0.010	+	Continuous	20/1	Decreased bacteria w/ + polarity	Acidity under active electrode
	Humans	0.010	−	Continuous	20/1		
Bolton[33] (1981)	Guinea pigs	0.020	+	Continuous	24/8	Cu electrode = decreased bacteria	
			−	Continuous	24/8		
Wilson[24] (1981)	Rats	1.58	+	Continuous	24/28	No effect on tensile strength	
Alvarez[32] (1983)	Pigs	0.004	−	Continuous	24/7	29% decrease in healing time, 109% increase in collagen	Increased fibroblast activity = increased collagen synthesis
Smith[13] (1984)	Mice	0.246	−	Continuous	24/50	No effect	Stimulates and enhances natural membrane potentials of skin
	Diabetic mice	0.246	−	Continuous	24/50	Tensile strength: 40% increase	
Steckel[23] (1984)	Horses	0.020	T	Continuous	24/28	No effect	Electrode insertion causes infection
Barron[6] (1985)	Humans	0.540	T	0.5 Hz Biphasic	1/9	92% decrease ulcer size @ 3 wk	Enhances potential and reduces ions needed for bacterial growth
Nannmark[19] (1985)	Rodents	1.61	+	Continuous	1.3/1	All modes = increased vascularity	
	Rodents	1.61	−	Continuous	1.3/1		
	Rodents	0.645 RMS	AC	Sine wave	1.3/1		
Fakhri[4] (1987)	Humans	3.60	T	Continuous	0.2/14–90	Improved healing of skin grafts and chronic burns	Enhances potential and reduces bacterial adhesion
Brown[10] (1987)	Rabbits	0.011 PK	−	0.80% Sawtooth	4/4	36% increase in tensile strength	Stimulation initially enhanced wounded skin potentials, later retarded wounded skin potentials
	Rabbits	0.011 PK	−	0.80% Sawtooth	4/7	30% increase in healing time	
Kloth[7] (1988)	Humans	0.168	+/−	1.05% Square wave	0.75/37	56.4% increase healing rate	
Sisken[28] (1988)	Rats	0.574 RMS	AC	Continuous	24/21	19% increased collagen	
	Rats	0.574 RMS	AC	Pulsed 50% sine wave	12/21	30% increase in vascularity	
Stromberg[14] (1988)	Pigs	0.338	−/+	1.28% square wave	1/14	40% decrease wound size	
			−	1.28% square wave	1/14	35% increase wound size	
Weiss[15] (1989)	Humans	0.514	+	1.92% square wave	1/7	54% decrease keloid scarring	
Davis[21] (1989)	Pigs	0.502	−/+	1.79% square wave	1/7	19.3% increase healing rate	
	Pigs	0.502	+	1.79% square wave	1/7	8.3% increase healing rate	

+: active electrode is over the wound; −: return electrode is over the wound; T (Tangential): wound is between the active and return electrode; AC: electrodes alternate being active.

This literature review summarized in Table 1 surveys the recent *in vivo* literature on stimulation of wounds with either direct or alternating current. It attempts to provide all the relevant parameters for comparison or reproduction. The electric parameters include the polarity, the average spatial current density, and the equivalent duty cycle (with waveform). The nonelectrical parameters include the animal model, duration or schedule of treatment, length of treatment, measures for evaluation, and a brief synopsis of results.

This review, as mentioned, is not complete. It only includes studies from the last 10 years. In addition, many of the studies did not report sufficient parameters to allow reproducibility. In some cases either the author or source of the equipment could be reached to ascertain important information. In other studies, particularly the earlier ones, this was not possible. Many studies contain unique experimental conditions or results, which cannot be condensed into a few words. Although there has been an attempt to resolve this in the footnotes, direct reference to the original is recommended.

Discussion

The literature on electric wound healing reflects a variety of conclusions regarding the best parameters

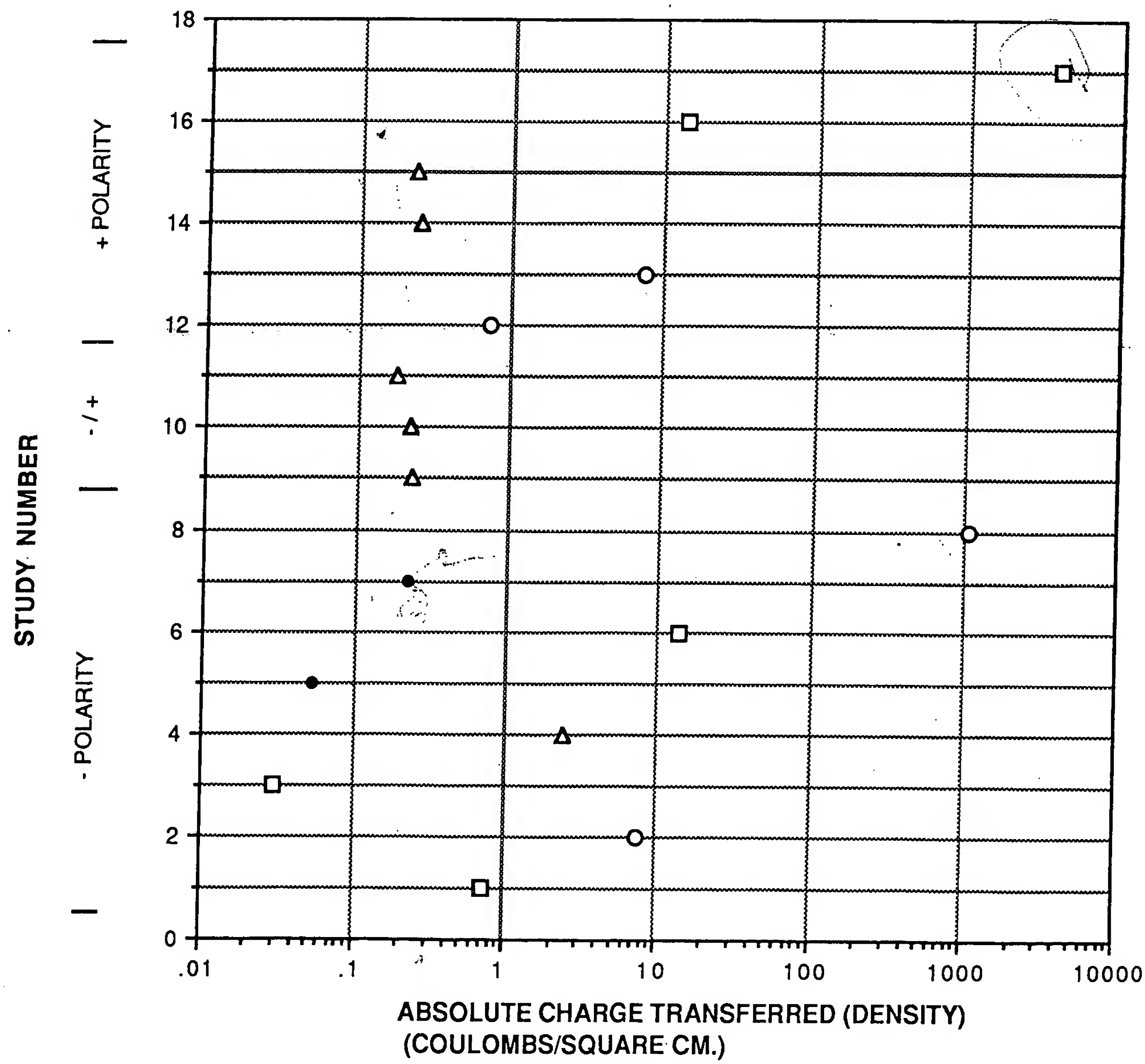

FIG. 1. Comparison of DC and pulsatile studies by polarity and charge transfer. Study number refers to Table 2. ●: Adverse effect; □: no effect; O: effective; Δ: highly effective.

for treatment. Among these conclusions is that pulsed electrical stimulation is superior to others. Pulsed electrical stimulation is assumed to allow higher current densities without tissue irritation or burning. It has been claimed that by using pulsed current and keeping the temporal average current output constant one can use a higher current intensity than with constant current.[26,27] Pulsed electrical stimulation also has been claimed to improve vascular support compared with constant stimulation.[16,19,28] It has been reported that pulsed electrical stimulation slightly above 32 Hz provides the greatest vascular support. Lower frequency pulsed electrical stimulation (<8 Hz) provided less vascular support, and this effect was most pronounced when coupled with positive polarity.[29] Negative polarity is reported to be best for improving vascularity. This is the reason many studies report it to be best early in treatment.[10,14,16,19,21,29,30,34]

Studies using pulsed electrical stimulation have concluded that negative polarity early in treatment is effective when followed by positive polarity later in treatment.[2,10,14,16,21,30] This vascular support is a possible reason for negative polarity being most effective early in treatment. Increased vascularity increases nu-

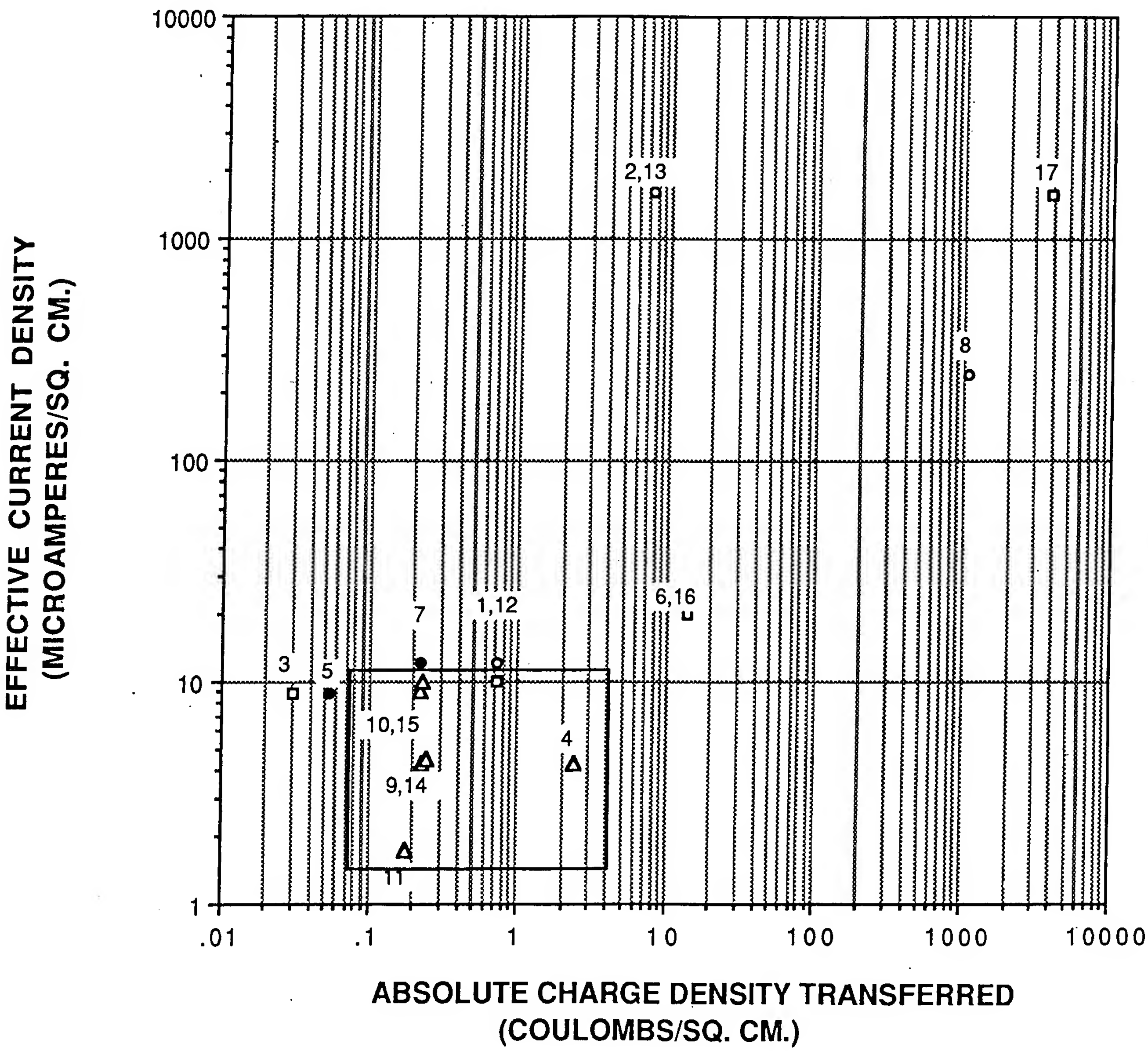

FIG. 2. Optimum dosage effective: current density versus absolute charge density transferred. Study number refers to Table 2. ●: Adverse effect; □: no effect; O: effective; Δ: highly effective; ▭: most effective region.

trient exchange necessary for successful wound healing.[5,16] Positive pulsed polarity is believed to increase comfort by decreasing nerve irritation.[16,30] Additional effects ascribed to positive polarity are improved oxygen delivery to the wound site, bactericide, and epithelialization.[10,26,30]

In order to evaluate these conclusions, this review compared the previous studies based on absolute charge density transferred (Fig. 1). This parameter is obtained by multiplying the average spatial current density by the effective dute cycle (duty cycle = 1 for constant nonpulsatile current) and by the total duration of treatment. The absolute charge density transferred is thus the amount of current delivered (A/cm^2) multiplied by the time of the treatment. This gives the total amount of charge delivered per unit area (coulombs $[C]/cm^2$).

The comparison shows that studies have been done with charge transfers ranging over six orders of magnitude. This indicates that there may be little to compare among the various studies. Because the literature is too variable, it is difficult to verify any of the previous conclusions.

Figure 2 presents the studies in terms of the absolute charge density transferred and the effective current density. The relationship between these two parameters enables us to arrive at the best treatment "dosage" because the current density tells us how much current should be applied, and the charge density transferred tells us how long this current should be applied. Together they describe a region where electrical stimulation has shown promise.

Analyzing Figures 1 and 2 enables us to draw two conclusions. First, it appears that varying the polarity is more effective in speeding wound healing than maintaining either polarity for the length of treatment. It was observed that there is a natural change in wound potentials from positive to negative during healing; therefore, it was proposed that changing polarity would enhance healing.[31] Table 2 shows that the three reproducible studies using alternating polarity provided significantly improved wound healing and one irreproducible study also confirmed this conclusion.[7,14,21,30] Another study that did not use alternating polarities and did not get improved healing attributed the inadequate results to using only one polarity.[10] Second, there is a trend that an absolute charge density transfer on the order of 0.1–2.0 C/cm^2 may be effective. Of the six studies performed in this range, five showed highly significant results. The one study that did poorly in this range was by Stromberg who used only negative polarity for 2 weeks.[14] All the other studies in this charge transfer range used either varied polarity or positive polarity. This is hardly conclusive evidence; however, it is a trend worth continued investigation. There are substantial zones in the two-dimensional range that have not been explored; hence, all we can conclude is that the rectangular region shows promise. The optimal zone may lie elsewhere, if indeed there is an optimal zone for all patients and wounds.

Although Figure 2 yields the optimal duration of treatment, it gives no indication of how this time should be scheduled. Of the studies that used 24-hour stimulation periods, only one showed improvement in healing.[16,32,33] It remains to be evaluated if 24-hour stimulation periods are effective. In general, the determination of the optimal time period is a needed area of future research.

Unfortunately, the studies that used either alternating current or tangential direct current cannot be compared meaningfully on the basis of absolute charge transferred. Therefore, they have not been included in Figure 1. Both techniques have been effective, and a study that compared direct alternating polarity treatment to either tangential current or alternating current of the equivalent parameters would certainly be enlightening.

To improve the consistency of future studies several guidelines are recommended. First, average spatial

TABLE 2. *Studies Compared in Figures 1 and 2*

Study No. Reference	Polarity	Treatment Parameters (Current Density,* hours, days)
1. Bolton[25]	Negative	0.01 mA/cm^2, 20, 1
2. Nannmark[19]	Negative	1.61 mA/cm^2, 1.3, 1
3. Brown[10]	Negative	0.011 mA/cm^2, 4, 4
4. Alvarez[32]	Negative	0.004 mA/cm^2, 24, 7
5. Brown[10]	Negative	0.011 mA/cm^2, 4, 7
6. Bolton[33]	Negative	0.02 mA/cm^2, 24, 8
7. Stromberg[14]	Negative	0.338 mA/cm^2, 1, 14
8. Smith[13]	Negative	0.246 mA/cm^2, 24, 50
9. Stromberg[14]	Alternating	0.338 mA/cm^2, 1, 14
10. Davis[21]	Alternating	0.502 mA/cm^2, 1, 7
11. Kloth[7]	Alternating	0.168 mA/cm^2, 0.75, 37
12. Bolton[25]	Positive	0.01 mA/cm^2, 20, 1
13. Nannmark[19]	Positive	1.61 mA/cm^2, 1.3, 1
14. Weiss[15]	Positive	0.249 mA/cm^2, 1, 7
15. Davis[21]	Positive	0.502 mA/cm^2, 1, 7
16. Bolton[33]	Positive	0.02 mA/cm^2, 24, 28
17. Wilson[24]	Positive	6.31 mA/cm^2, 24, 28

* Current density is the absolute spatial current density. For pulsed stimulation studies,[7,10,14,21] Figure 2 uses the effective current density, which is the absolute spatial current density multiplied by the duty cycle.

current density (with respect to time) and duty cycle should always be reported. The authors should also report the polarity, wavelength, and time patterns of treatment. Second, the density of the absolute value of the charge density transferred should always be calculated and compared with previous studies to determine whether any study is comparable. It is hoped that future research will continue to focus on certain regions of charge density transfer in which electrical stimulation seems promising.

Conclusion

This literature review provides three conclusions. First, two electric parameters can be established that allow easy reproducibility and comparison with previous studies. These two parameters are the average spatial current density and the effective duty cycle. These parameters can be combined with the treatment time to provide the absolute charge density transferred. The authors recommend that future stimulation studies employ these parameters. Second, a comparison of the previous studies indicates that alternating polarities (negative initially) is more effective than maintaining either positive or negative polarity for the entire treatment period. The exact polarity sequence remains to be verified. Third, the literature indicates that an absolute charge transfer between 0.1 and 2.0 C/cm^2 appears to be effective. This conclusion is only a recommendation based on an observed trend. There are only a handful of studies that verify this range, and large regions of charge transfer have never been studied. We encourage future research be done in this area.

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